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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/574,386	05/19/00	ALBERTSON D	M-9144 US

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1656	5

DATE MAILED: 12/22/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/574,386	ALBERTSON ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Specification

1. The disclosure is objected to because of the following informalities:

A) Page 6, ln. 27, recites "microarry", which should be amended to recite "microarray".

Appropriate correction is required.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 3-13, and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith (PCR Methods and Applications (1992) 2: 21-27, cited in the IDS).

Smith teaches ligation-mediated PCR of restriction fragments from large DNA molecules. The reference teaches a method of PCR that involves sequence-specific ligation of "adapter-tags", which provide a target for primer annealing subsequent PCR reactions (abstract). Another adapter (i.e. "bubble-tags") provide a second target for primer annealing (abstract). Smith teaches that the advantage of this method is that specific fragments can be isolated without any prior knowledge of the nucleotide sequence of the target (abstract). Furthermore, the reference teaches that the method provides a means to amplify fragments of any DNA molecule ranging from about 50 to 25 kb in size (pg. 21). The reference also teaches that the "adapter-tags" contain a second strand having a region of substantial complementarity to a region of the first strand (pg. 21-22, Table 1). The reference also teaches that the amplification product can be

isolated (pg. 24), and can then be resuspended to form a target solution. The claims recite "preparing amplification products useful for forming an array" and "resuspending each amplification product to form a target solution suitable for application to a substrate". The claims do not specifically require performing an active process step of applying the amplification products to a substrate. Also, it is a property of Smith's target solution comprising amplification products, that this target solution would be suitable for application to a substrate. Smith also teaches that the ligase-mediated PCR technique can be used from polynucleotides derived from large molecules, such as YAC (pg. 25). With respect to claim 10, the reference teaches the use of a type IIS restriction endonucleases (abstract). With respect to claims 11-13, the reference teaches that sequence runs of 350 basepairs were used.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 2, 14-16 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (PCR Methods and Applications (1992) 2: 21-27, cited in the IDS), in view of Brown et al. (US 5,807,522, cited in the IDS).

Smith teaches ligation-mediated PCR of restriction fragments from large DNA molecules. The reference teaches a method of PCR that involves sequence-specific ligation of "adapter-tags", which provide a target for primer annealing subsequent PCR reactions (abstract). Another adapter (i.e. "bubble-tags") provide a second target for primer annealing (abstract).

Smith teaches that the advantage of this method is that specific fragments can be isolated without any prior knowledge of the nucleotide sequence of the target (abstract). Furthermore, the reference teaches that the method provides a means to amplify fragments of any DNA molecule ranging from about 50 to 25 kb in size (pg. 21). The reference also teaches that the "adapter-tags" contain a second strand having a region of substantial complementarity to a region of the first strand (pg. 21-22, Table 1). The reference also teaches that the amplification product can be isolated (pg. 24), and can then be resuspended to form a target solution. Smith also teaches that the ligase-mediated PCR technique can be used from polynucleotides derived from large molecules, such as YAC (pg. 25). In addition, Smith teaches that this method can be used in fingerprinting cosmids, YACS, and bacterial genomes or could be used for multiplex chromosome walking in clone libraries arrayed in high density grids (pg. 26). Smith does not teach using amplification products to generate an array.

Brown et al. teach methods for fabricating microarrays of biological samples. Smith teaches an apparatus for forming microarrays comprising; dispensing a known volume of a reagent at each selected array position, by tapping a capillary dispenser onto a support under conditions effective to draw a defined volume of liquid onto the support (abstract). The reference teaches that microarrays can be used in hybridizations assays, genetic and physical mapping of genomes, monitoring of gene expression, DNA sequencing, genetic diagnosis, genotyping of organisms, etc. (col. 14, ln. 35 to col. 15). The reference also teaches an example of using PCR amplified array elements in the microarray (col. 16-17). Furthermore, the reference teaches that the volume of each target applied to the substrate is 0.01 to 100 nanoliters

(col. 3, ln. 39-41). The reference also teaches that the array comprises at least 1000 amplification products in a 1 cm^2 region of substrate (col. 4, ln. 16-19).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Smith so as to have applied the target solution comprising the amplified fragments to the microarray of Brown in order to have achieved the benefits of producing an array useful for fingerprinting large molecules such as YACSs, cosmids, and bacterial genomes by DNA sequencing and gene expression analysis.

6. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (PCR Methods and Applications (1992) 2: 21-27, cited in the IDS), in view of Brown et al. (US 5,807,522, cited in the IDS), and in further view of Gordon et al. (US 5,601,980).

The teachings of Smith and Brown are presented above. The references do not teach the spotting of the target solutions on the substrate.

Gordon et al. teaches a manufacturing method and apparatus for biological probe arrays using vision-assisted micropipetting. Specifically, Gordon teaches a robotically manipulated micropipette which is used for spotting biological samples onto an array (col. 3, ln. 59-60).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Smith and Brown so as to have robotically spotted target solutions onto the substrate (i.e. array) in order to have achieved the benefits stated by Gordon of providing an accurate and cost effective spotting of miniscule volumes of biological material onto a substrate.

7. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (PCR Methods and Applications (1992) 2: 21-27, cited in the IDS), in view of Brown et al. (US

5,807,522, cited in the IDS), and further in view of Stimpson et al. (Proc. Natl. Acad. Sci. USA (1995) 92: 6379-6383).

The teachings of Smith and Brown are presented above. The references do not teach the method wherein at least one of the adapters includes an amino group.

Stimpson teaches the method of real-time detection of DNA hybridization and melting on oligonucleotide arrays by using optical wave guides. Specifically, Stimpson teaches DNA chips (i.e. array), which are constructed by using 3'-amino-labeled oligonucleotides (pg. 6380). Furthermore, Stimpson teaches that these amino-labeled oligonucleotides are immoblizied onto the chip (6380).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Smith and Brown so as to have added an amino group to the adapter so as to have aided in the immobilization of the amplified polynucleotide onto the array.

8. Claims 19 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith (PCR Methods and Applications (1992) 2: 21-27, cited in the IDS), in view of Cronin et al. (WO 97/43450)

The teachings of Smith are presented above. The references do not teach resuspending the target solutions with dimethyl sulfoxide at a concentration of 20% by volume.

Cronin teaches hybridization assays on oligonucleotide arrays. Cronin teaches the method of performing a hybridization assay between a target nucleic acid molecule and an oligonucleotide array (comprising a plurality of discrete locations), wherein the array is incubated with a hybridization mixture comprising the target nucleic acid and a hybridization

optimizing agent (pg. 17, ln. 1-8). The reference further teaches that the optimizing agent can be a denaturing agent (i.e. DMSO) (pg. 18, ln. 6-11). The reference teaches that denaturing agents lower the melting temperatures of double stranded nucleic acid molecules by interfering with hybdrogen bonding between bases in a double stranded nucleic acid (pg. 5, ln. 31-33), therefore improving signal resolution in hybridization assays performed on substrate bound oligonucleotide arrays (pg. 2, ln. 14-17). The reference also teaches a range of concentrations of denaturing agents that can used for the hybridization mixture pg. 6, ln. 1-2).

One of ordinary skill in the art would have been motivated to use the method of Smith to produce a target solution comprising dimethyl sulfoxide at a concentration of 20%, in order to provide a more effective hybridization assay to be performed on substrate bound oligonucleotide. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Smith of producing a target solution comprising dimethyl sulfoxide at a concentration of 20%, to provide a target solution suitable for application to an array of polynucleotides. While Cronin does not specifically teach a method using a concentration of 20% dimethyl sulfoxide, it is well known and common knowledge in the art that one of ordinary skill would use a solution of dimethyl sulfoxide at a concentration of 20% to optimize the hybridization reaction based on the concentration of the target nucleic acid and other reagents comprising the target solution.

Conclusion

9. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (703) 305-0806. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Alexander H. Spiegler
December 14, 2000

CARLA J. MYERS
PRIMARY EXAMINER